General

Guideline Title

Treatment of symptoms of the menopause: an Endocrine Society clinical practice guideline.

Bibliographic Source(s)

Stuenkel CA, Davis SR, Gompel A, Lumsden MA, Murad MH, Pinkerton JV, Santen RJ. Treatment of symptoms of the menopause: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015 Nov;100(11):3975-4011. [368 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (+OOO, ++OO, +++O, and ++++); the strength of the recommendation (1 or 2); and the difference between a "recommendation" and a "suggestion" are provided at the end of the "Major Recommendations" field.

Diagnosis and Symptoms of Menopause

The Task Force suggests diagnosing menopause based on the clinical criteria of the menstrual cycle. (2|++OO)

If establishing a diagnosis of menopause is necessary for patient management in women having undergone a hysterectomy without bilateral oophorectomy or presenting with a menstrual history that is inadequate to ascertain menopausal status, the Task Force suggests making a presumptive diagnosis of menopause based on the presence of vasomotor symptoms (VMS) and, when indicated, laboratory testing that includes replicate measures of follicle-stimulating hormone (FSH) and serum estradiol. (2|++OO)

Health Considerations for All Menopausal Women

When women present during the menopausal transition, the Task Force suggests using this opportunity to address bone health, smoking cessation, alcohol use, cardiovascular risk assessment and management, and cancer screening and prevention. (Ungraded best practice statement)

Hormone Therapy for Menopausal Symptom Relief

Estrogen and Progestogen Therapy

For menopausal women <60 years of age or <10 years past menopause with bothersome VMS (with or without additional climacteric symptoms)

who do not have contraindications or excess cardiovascular or breast cancer risks and are willing to take menopausal hormone therapy (MHT), the Task Force suggests initiating estrogen therapy (ET) for those without a uterus and estrogen plus progestogen therapy (EPT) for those with a uterus. (2|++OO)

Cardiovascular Risk

For women <age 60 or <10 years past menopause onset considering MHT for menopausal symptom relief, the Task Force suggests evaluating the baseline risk of cardiovascular disease (CVD) and taking this risk into consideration when advising for or against MHT and when selecting type, dose, and route of administration. (2|++OO)

For women at high risk of CVD, the Task Force suggests initiating nonhormonal therapies to alleviate bothersome VMS (with or without climacteric symptoms) over MHT. (2|++OO)

For women with moderate risk of CVD, the Task Force suggests transdermal estradiol as first-line treatment, alone for women without a uterus or combined with micronized progesterone (or another progestogen that does not adversely modify metabolic parameters) for women with a uterus, because these preparations have less untoward effect on blood pressure, triglycerides, and carbohydrate metabolism. (2|++OO)

Venous Thromboembolic Events

For women at increased risk of venous thromboembolism (VTE) who request MHT, the Task Force recommends a nonoral route of ET at the lowest effective dose, if not contraindicated (1|++OO); for women with a uterus, the Task Force recommends a progestogen (for example, progesterone and dydrogesterone) that is neutral on coagulation parameters. (1|+++O)

Breast Cancer

For women considering MHT for menopausal symptom relief, the Task Force suggests evaluating the baseline risk of breast cancer and taking this risk into consideration when advising for or against MHT and when selecting type, dose, and route of administration. (2|++OO)

For women at high or intermediate risk of breast cancer considering MHT for menopausal symptom relief, the Task Force suggests nonhormonal therapies over MHT to alleviate bothersome VMS. (2|++OO)

Tailoring MHT

The Task Force suggests a shared decision-making approach to decide about the choice of formulation, starting dose, the route of administration of MHT, and how to tailor MHT to each woman's individual situation, risks, and treatment goals. (Ungraded best practice statement)

Custom-compounded Hormones

The Task Force recommends using MHT preparations approved by the US Food and Drug Administration (FDA) and comparable regulating bodies outside the United States and recommend against the use of custom-compounded hormones. (Ungraded best practice statement)

Conjugated Equine Estrogens with Bazedoxifene

For symptomatic postmenopausal women with a uterus and without contraindications, the Task Force suggests the combination of conjugated equine estrogens (CEE)/bazedoxifene (BZA) (where available) as an option for relief of VMS and prevention of bone loss. (2|+++O)

Tibolone

For women with bothersome VMS and climacteric symptoms and without contraindications, the Task Force suggests tibolone (in countries where available) as an alternative to MHT. (2|++OO)

The Task Force recommends against adding tibolone to other forms of MHT. (1|++OO)

The Task Force recommends against using tibolone in women with a history of breast cancer. (1|++OO)

Clinical Management of Patients Taking Hormone Therapies

Monitoring During Therapy

For women with persistent unscheduled bleeding while taking MHT, the Task Force recommends evaluation to rule out pelvic pathology, most importantly, endometrial hyperplasia and cancer. (1|+++O)

The Task Force recommends informing women about the possible increased risk of breast cancer during and after discontinuing EPT and

emphasizing the importance of adhering to age-appropriate breast cancer screening. (1|+++O)

The Task Force suggests that the decision to continue MHT be revisited at least annually, targeting the shortest total duration of MHT consistent with the treatment goals and evolving risk assessment of the individual woman. (Ungraded best practice statement)

For young women with primary ovarian insufficiency (POI), premature or early menopause, without contraindications, the Task Force suggests taking MHT until the time of anticipated natural menopause, when the advisability of continuing MHT can be reassessed. (2|++OO)

Stopping Considerations

For women preparing to discontinue MHT, the Task Force suggests a shared decision-making approach to elicit individual preference about adopting a gradual taper vs. abrupt discontinuation. (2|++OO)

Nonhormonal Therapies for VMS

For postmenopausal women with mild or less bothersome hot flashes, the Task Force suggests a series of steps that do not involve medication, such as turning down the thermostat, dressing in layers, avoiding alcohol and spicy foods, and reducing obesity and stress. (2|++OO)

Nonhormonal Prescription Therapies for VMS

For women seeking pharmacological management for moderate to severe VMS for whom MHT is contraindicated, or who choose not to take MHT, the Task Force recommends selective serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs) or gabapentin or pregabalin (if there are no contraindications). (1|+++O)

For those women seeking relief of moderate to severe VMS who are not responding to or tolerating the nonhormonal prescription therapies, SSRIs/SNRIs or gabapentin or pregabalin, the Task Force suggests a trial of clonidine (if there are no contraindications). (2|++OO)

Over-the-Counter and Alternative Nonhormonal Therapies for VMS

For women seeking relief of VMS with over-the-counter (OTC) or complementary medicine therapies, the Task Force suggests counseling regarding the lack of consistent evidence for benefit for botanicals, black cohosh, omega-3-fatty acids, red clover, vitamin E, and mind/body alternatives including anxiety control, acupuncture, paced breathing, and hypnosis. (2|++OO)

Treatment of Genitourinary Syndrome of Menopause

Vaginal Moisturizers and Lubricants

For postmenopausal women with symptoms of vulvovaginal atrophy (VVA), the Task Force suggests a trial of vaginal moisturizers to be used at least twice weekly. (2|++OO)

For women who do not produce sufficient vaginal secretions for comfortable sexual activity, the Task Force suggests vaginal lubricants. (2|++OO)

Vaginal Estrogen Therapies

For women without a history of hormone- (estrogen) dependent cancers who are seeking relief from symptoms of genitourinary syndrome of menopause (GSM) (including VVA) that persist despite using vaginal lubricants and moisturizers, the Task Force recommends low-dose vaginal ET. (1|+++O)

Practice Statement

In women with a history of breast or endometrial cancer who present with symptomatic GSM (including VVA) that does not respond to nonhormonal therapies, the Task Force suggests a shared decision-making approach that includes the treating oncologist to discuss using low-dose vaginal ET. (Ungraded best practice statement)

For women taking raloxifene, without a history of hormone- (estrogen) dependent cancers, who develop symptoms of GSM (including VVA) that do not respond to nonhormonal therapies, the Task Force suggests adding low-dose vaginal ET. (2|++OO)

For women using low-dose vaginal ET, the Task Force suggests against adding a progestogen (i.e., no need for adding progestogen to prevent endometrial hyperplasia). (2|+OOO)

For women using vaginal ET who report postmenopausal bleeding or spotting, the Task Force recommends prompt evaluation for endometrial pathology. (1|++OO)

Ospemifene

For treatment of moderate to severe dyspareunia associated with vaginal atrophy in postmenopausal women without contraindications, the Task Force suggests a trial of ospemifene. (2|+++O)

For women with a history of breast cancer presenting with dyspareunia, the Task Force recommends against ospemifene. (1|+OOO)

Definitions

Quality of Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

Strength of Recommendation

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

Clinical Algorithm(s)

An algorithm titled "Approach to the Patient with VMS Contemplating MHT" is provided in the original guideline document.

Scope

Disease/Condition(s)

Menopause

Note: The detailed management of early menopause transition, primary ovarian insufficiency, and prevention of osteoporosis and fracture are considered beyond the current scope.

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Endocrinology

Family Practice

Internal Medicine

Obstetrics and Gynecology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To generate a practice guideline for the management and treatment of symptoms of the menopause

Target Population

Women with symptoms of menopause

Interventions and Practices Considered

1. Diagnosis
    - Based on clinical criteria
    - Presumptive diagnosis (women having undergone hysterectomy without bilateral oophorectomy or presenting with a menstrual history that is inadequate to ascertain menopausal status)
2. Consideration of other health factors (smoking, bone health, alcohol use, cardiovascular health, cancer screening)
3. Menopausal hormone therapy (MHT)
    - Estrogen therapy (ET)
    - Estrogen plus progestogen therapy (EPT)
    - Conjugated estrogen plus bazedoxifene
    - Clinical management (monitoring and stopping)
4. Nonhormonal therapies for vasomotor symptoms (VMS)
    - Non-medication steps (e.g., dressing in layers, reducing obesity and stress)
    - Nonhormonal prescription therapies (selective serotonin reuptake inhibitors [SSRIs]/serotonin-norepinephrine reuptake inhibitors [SNRIs], gabapentin, pregabalin)
    - Counseling patient on lack of consistent evidence for the benefit of nonhormonal over-the-counter and alternative therapies
5. Treatment of genitourinary syndrome
    - Vaginal moisturizers and lubricants
    - Low-dose vaginal ET
    - Ospemifene

Major Outcomes Considered

- Cardiovascular heart disease
- Invasive breast cancer
- Thrombotic events, including stroke, pulmonary embolism, and deep vein thrombosis
- Other cancers, including colorectal cancer, endometrial cancer, and lung cancer
- All fractures, including hip fractures
- All cause mortality
- Diabetes

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The Task Force reviewed primary evidence and commissioned three additional systematic reviews (see the "Availability of Companion Documents" field) to support the guideline.

Oral vs. Transdermal Estrogen and the Risk of Venous and Arterial Thrombotic Adverse Events: A Systematic Review and Meta-analysis

The reviewers included original prospective and retrospective studies that enrolled postmenopausal women using either oral or transdermal hormone replacement therapy (HRT) and reported the outcome of interest (risk of venous thromboembolism [VTE], pulmonary embolism [PE], deep venous thrombosis [DVT], myocardial infarction [MI] and cerebrovascular events). The studies included should report using of both oral and transdermal HRT. The reviewers excluded case series or uncontrolled studies and articles reported only either oral or transdermal HRT use.

The search included a comprehensive search of several databases from each database's earliest inception to August 2013, any language was conducted. The databases included Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The studies search was conducted by an experienced Mayo Clinic librarian. Controlled vocabulary supplemented with keywords was used to search for comparative studies of oral vs. transdermal estrogen and the risk of venous and arterial thrombotic events (see Appendix 1 in the systematic review for detailed search strategy).

Abstracts and titles that resulted from executing the search strategy were independently evaluated by two reviewers for potential eligibility and the full text versions of all potentially eligible studies were obtained. Two reviewers working independently considered the full text reports for eligibility. Disagreements were harmonized by consensus and if not possible by consensus through arbitration by a third reviewer.

Risk of Breast Cancer in Natural Progesterone Versus Synthetic Progestins: A Systematic Review and Meta-analysis

The reviewers included comparative studies that compared natural progesterone with any of the synthetic progestins in postmenopausal women who are less than ten years of menopause or their age is 50-59. Only the studies that had a follow up period ≥6 months and reported any of the following outcomes: breast cancer cases, breast cancer incidence and prevalence and cardiac events were eligible for inclusion.

The search included the electronic databases of MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews and Scopus. The reviewers expanded the search to include all languages, with latest date of inclusion to be August 2013. Abstracts and titles that resulted from executing the search strategy were independently evaluated by two reviewers for potential eligibility and the full text versions of all potentially eligible studies were obtained. Two reviewers working independently considered the full text reports for eligibility. Disagreements were harmonized by consensus and if not possible by consensus through arbitration by a third reviewer.

Hormonal Replacement Therapy and Mortality: A Systematic Review and Meta-analysis

The reviewers included original prospective and retrospective comparative studies that enrolled postmenopausal women using HRT and reported the outcome of interest (all-cause mortality). The reviewers excluded case series or uncontrolled studies and articles reported follow up less than 6 months.

The search included a comprehensive search of several databases from each database's earliest inception to August 2013, no language restriction was conducted. The databases included Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced Mayo Clinic librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for comparative studies of postmenopausal women using HRT and associated mortality (see Appendix 1 in the systematic review for the detailed search strategy).

Abstracts and titles that resulted from executing the search strategy were independently evaluated by two reviewers for potential eligibility and the full text versions of all potentially eligible studies were obtained. Two reviewers working independently considered the full text reports for eligibility. Disagreements were harmonized by consensus and if not possible by consensus through arbitration by a third reviewer.

Number of Source Documents

Oral vs. Transdermal Estrogen and the Risk of Venous and Arterial Thrombotic Adverse Events: A Systematic Review and Meta-analysis

The initial search resulted in 619 citations and after abstract screening the reviewers identified 87 potentially relevant studies and 3 more were identified through reference review of the selected articles. After full text reviewing, they included 14 studies while excluding 76 studies for reasons mentioned in Figure 1 in the systematic review (see the "Availability of Companion Documents" field). The original study design in 9 studies was case-control studies, 5 studies were cohort studies and no studies were clinical trials.

Risk of Breast Cancer in Natural Progesterone Versus Synthetic Progestins: A Systematic Review and Meta-analysis

The initial search resulted in 2953 citations. After screening the abstracts, this was limited to 46 potentially relevant articles. These were reviewed in full-text by two authors and eventually 2 studies were included with 44 being excluded for reasons mentioned in Figure 1 in the systematic review (see the "Availability of Companion Documents" field). Both studies were cohort studies. None of the studies addressed the risk of cardiovascular disease.

Hormonal Replacement Therapy and Mortality: A Systematic Review and Meta-analysis

The initial search resulted in 2244 citations and after abstract screening the reviewers identified 320 potentially relevant studies and 19 more were identified through reference review of the selected articles. After full text reviewing, the reviewers included 96 studies while excluding 243 studies for reasons mentioned in Figure 1 in the systematic review (see the "Availability of Companion Documents" field). The original study design in 38 studies was randomized controlled trials (RCTs), 52 studies were cohort design and 6 were case-control studies.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The Task Force reviewed primary evidence and commissioned three additional systematic reviews (see the "Availability of Companion Documents" field) to support the guideline.

Oral vs. Transdermal Estrogen and the Risk of Venous and Arterial Thrombotic Adverse Events: A Systematic Review and Meta-analysis

Using a standardized form two reviewers independently extracted data from each study and later reconciled differences, if present. The reviewers determined the methodological quality of studies and collected descriptive, methodological and outcome data. For assessing the risk of bias, the reviewers used The Newcastle-Ottawa Scale (NOS) to appraise the risk of bias of the included case-control and cohort studies.

For dichotomized outcomes, the reviewers calculated risk ratio from comparing oral hormone replacement therapy (HRT) versus transdermal HRT in the included studies. The 95% confidence intervals (CIs) were estimated using binomial distribution. The reviewers then pooled the log transformed risk ratios using the DerSimonian and Laird random-effect models with the heterogeneity estimated from the Mantel-Haenszel model.

The reviewers conducted subgroup analyses based on outcome, estrogen dose and type. To measure the overall heterogeneity across the included studies, the reviewers used I^2 statistic, where I^2>50% suggests high heterogeneity. All statistical analyses were conducted using CMA version 2.

Risk of Bias Assessment

The overall risk of bias in the included observational studies was moderate; samples were representative in most studies together with no baseline imbalance and nearly all the studies adjusted for at least one important confounder.

See the systematic review for further information on the risks associated with specific outcomes.

Subgroup Analysis

Subgroup analysis was only possible for the outcome of venous thromboembolism (VTE). There was no significant interaction between the dose of estrogen or the type of HRT (estrogen vs. combined) and the risk of VTE.

Risk of Breast Cancer in Natural Progesterone Versus Synthetic Progestins: A Systematic Review and Meta-analysis

Using a standardized form two reviewers independently extracted data from each study and later reconciled differences, if present. The reviewers determined the methodological quality of studies using NOS and collected descriptive, methodological and outcome data.

Risk of Breast Cancer

Based on meta-analysis of the 2 studies, natural progesterone was associated with lower breast cancer risk compared to synthetic progestin (Pooled risk ratio=0.67, [95% CI 0.55-0.81] I^2=42%).

Hormonal Replacement Therapy and Mortality: A Systematic Review and Meta-analysis

Using a standardized form two reviewers independently extracted data from each study and later reconciled differences, if present. The reviewers determined the methodological quality of studies and collected descriptive, methodological and outcome data.

For assessing the risk of bias, the reviewers used Cochrane tool for assessing randomized controlled trials (RCTs) and NOS to appraise the risk of bias of the included case-control, cohort and comparative case series studies.

For dichotomized outcomes, the reviewers calculated risk ratio from comparing HRT use vs. HRT non-use in the included studies. The 95% CIs were estimated using binomial distribution. The reviewers then pooled the log transformed risk ratios using the DerSimonian and Laird random-effect models with the heterogeneity estimated from the Mantel-Haenszel model.

The reviewers conducted subgroup analyses based on estrogen type (only estrogen vs. combined estrogen), preexisting condition and type of study design. To measure the overall heterogeneity across the included studies, they used I^2 statistic, where I^2>50% suggests high heterogeneity. All statistical analyses were conducted using CMA version 2.

Risk of Bias Assessment

In the randomized trials, the risk of bias was moderate to high. Randomization methods were unclear or not reported in 12 studies, 25 studies didn't report allocation concealment and blinding wasn't reported in 16 studies. The percentage lost to follow-up ranged from 0–46%. For observational studies, samples were representative in most studies together with no baseline imbalance; nearly all the studies adjusted for at least one important confounder and most of the studies didn't report the adequacy of follow up.

In subgroup analysis (limited to RCTs), there was no significant interaction based on hormone type (estrogen vs. combined) and based on whether patients had a pre-existing heart disease (P >0.05 for both).

See the systematic review for more information on HRT and mortality.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Participants

The Treatment of Symptoms of the Menopause Task Force included six experts, a methodologist, and a medical writer, all appointed by The Endocrine Society.

Evidence

The Task Force developed this evidenced-based guideline using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence. The Task Force commissioned three systematic reviews of published data and considered several other existing meta-analyses and trials.

Consensus Process

Multiple e-mail communications, conference calls, and one face-to-face meeting determined consensus. Committees of The Endocrine Society, representatives from endorsing societies, and members of The Endocrine Society reviewed and commented on the drafts of the guidelines. The Australasian Menopause Society, the British Menopause Society, European Menopause and Andropause Society, the European Society of Endocrinology, and the International Menopause Society (co-sponsors of the guideline) reviewed and commented on the draft.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendation

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Committees of The Endocrine Society, representatives from endorsing societies, and members of The Endocrine Society reviewed and commented on the drafts of the guidelines. The Australasian Menopause Society, the British Menopause Society, European Menopause and Andropause Society, the European Society of Endocrinology, and the International Menopause Society (co-sponsors of the guideline) reviewed and commented on the draft.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

In postmenopausal women, estrogen therapy (ET) improves menopause-associated (climacteric) symptoms (e.g., vasomotor symptoms [VMS], genitourinary symptoms, sleep disturbance, menopause-associated anxiety and depressive symptoms, and arthralgias). ET also reduces menopause-related bone loss, lowers the risk of fragility fractures in older women, and reduces the incidence of self-reported diabetes. In addition, combined estrogen plus progestogen therapy [EPT] reduced the risk of colorectal cancer and, in cumulative follow-up of the Women's Health Initiative (WHI), endometrial cancer.

Potential Harms

- See Table 4 in the original guideline document for specific cautions for the use of systemic menopausal hormone therapy (MHT) or selective estrogen receptor modulators (SERMs) for treatment of menopausal symptoms.
- Side effects of MHT can include abdominal/pelvic pain, mastalgia, metrorrhagia, weight gain, mood changes and blood pressure changes.
- Preliminary evidence suggests a possible increase in risk of bone fracture with selective serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs).
- Side effects of vaginal estrogens include vulvovaginal candidiasis and, with higher dosing and systemic absorption, vaginal bleeding and breast pain. Adverse effects include potential transfer to partner via penile or oral absorption and, with vaginal creams, residue on undergarments.
- The most common adverse effect of ospemifene was vasomotor symptoms (VMS) (7.2% of women taking ospemifene compared with 2% taking placebo).
- Although an osteoporosis trial found a 2-fold risk of venous thromboembolism (VTE) with bazedoxifene (BZA) 20-mg therapy alone, there was no additive effect on VTE when BZA was combined with conjugated equine estrogens (CEEs), although adequately powered studies are necessary.
- Gabapentin and pregabalin may increase suicidal thoughts and behaviors, cause drowsiness or dizziness, and impair balance and coordination. Pregabalin may impair memory and concentration.

Contraindications

Contraindications

- Clonidine is contraindicated in patients with low blood pressure and may cause light headedness, hypotension, headache, and constipation; sudden cessation of treatment can be associated with significant increments in blood pressure.
- See Table 4 in the original guideline document for specific cautions for the use of systemic menopausal hormone therapy (MHT) or selective estrogen receptor modulators (SERMs) for treatment of menopausal symptoms.
- Hypersensitivity or prior adverse drug reactions to nonhormonal prescription therapies represent contraindications. For the serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs), prior neuroleptic syndrome, serotonin syndrome, and concurrent use of monoamine oxidase inhibitors are also contraindications. SSRI/SNRIs should be used with caution in patients with bipolar disease, uncontrolled seizures, hepatic or renal insufficiency, uncontrolled hyponatremia, concurrent use of other SSRI/SNRIs, or poorly controlled hypertension. These agents uncommonly induce suicidal thoughts within the first few months of treatment.

Qualifying Statements

Qualifying Statements

- Clinical Practice Guidelines are developed to be of assistance to endocrinologists and other health care professionals by providing guidance and recommendations for particular areas of practice. The Guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The Guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The Guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of health care providers and each patient's individual circumstances.
- The Endocrine Society makes no warranty, express or implied, regarding the Guidelines and specifically excludes any warranties of

merchantability and fitness for a particular use or purpose. The Society shall not be liable for direct, indirect, special, incidental, or consequential damages related to the use of the information contained herein.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Stuenkel CA, Davis SR, Gompel A, Lumsden MA, Murad MH, Pinkerton JV, Santen RJ. Treatment of symptoms of the menopause: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015 Nov;100(11):3975-4011. [368 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Nov

Guideline Developer(s)

The Endocrine Society - Professional Association

Source(s) of Funding

Funding for this guideline was derived solely from The Endocrine Society, and thus the Task Force received no funding or remuneration from commercial or other entities.

Guideline Committee

The Treatment of Symptoms of the Menopause Task Force

Composition of Group That Authored the Guideline

Task Force Members: Cynthia A. Stuenkel (*Chair*), Susan R. Davis, Anne Gompel, Mary Ann Lumsden, M. Hassan Murad, JoAnn V. Pinkerton, Richard J. Santen

Financial Disclosures/Conflicts of Interest

The Endocrine Society maintains a rigorous conflict-of-interest review process for the development of clinical practice guidelines. All Task Force members must declare any potential conflicts of interest, which are reviewed before the members are approved to serve on the Task Force and periodically during the development of the guideline. The conflict-of-interest forms are vetted by the Clinical Guidelines Subcommittee (CGS) before the members are approved by the Society's Council to participate on the guideline Task Force. Participants in the guideline development must include a majority of individuals without conflict of interest in the matter under study. Participants with conflicts of interest may participate in the development of the guideline, but they must have disclosed all conflicts. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined by remuneration in any amount from the commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (e.g., stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers' bureaus, advisory boards, or boards of directors; or other financial benefits. Completed forms are available through the Endocrine Society office.

Financial Disclosures of the Task Force*

Cynthia A. Stuenkel, MD (Chair) – Financial or business/organizational interests: North American Menopause Society (Chair, Exam Committee), National Women's Law Center-Well Women's Project; Significant financial interest or leadership position: none declared.

Susan R. Davis, MBBS, PhD – Financial or Business/Organizational Interests: International Menopause Society, North American Menopause Society, Menopause, Maturitas, Climacteric, Trimel Pharmaceuticals Canada, Lawley Pharmaceuticals Australia, Abbott Pharmaceuticals; Significant Financial Interest or Leadership Position: International Menopause Society, National Health and Medical Research Council, Australia, Bupa Health Foundation.

Anne Gompel, MD, PhD – Financial or Business/Organizational Interests: European Society for Contraception, European Society of Endocrinology, Groupe d'Etude sur la Ménopause et le Vieillissement Hormonal, Société Française de Sénologie et Pathologie Mammaire; Significant financial interest or leadership position: none declared.

Mary Ann Lumsden, MD, PhD – Financial or Business/Organizational Interests: —Financial or Business/Organizational Interests: International Menopause Society, British Menopause Society; Significant Financial Interest or Leadership Position: National Institute of Health and Care Excellence.

M. Hassan Murad, MD, MPH** – Financial or business/organizational interests: Mayo Clinic, Division of Preventive Medicine; Significant financial interest or leadership position: none declared.

JoAnn V. Pinkerton, MD – Financial or business/organizational interests: North American Menopause Society, Menopause Journal, OBG

Management, Climacteric Journal, Journal of Women's Health, University of Virginia Board of Visitors (Noven Pharmaceuticals, Pfizer, Inc., Shionogi, Therapeutics MD), University of Virginia Clinical Trials (Therapeutics MD); Significant Financial Interest or Leadership Position: North American Menopause Society, Academy of Women's Health, South Atlantic Association of ObGyn.

Richard J. Santen, MD – Financial or business/organizational interests: American Society of Clinical Oncology, Up-to-Date (Author/Honorarium); Significant Financial Interest or Leadership Position: Pfizer (Advisory Board, Research Grant).

*Financial, business, and organizational disclosures of the Task Force cover the year prior to publication. Disclosures prior to this time period are archived.

**Evidence-based reviews for this guideline were prepared under contract with The Endocrine Society.

Guideline Endorser(s)

Australasian Menopause Society - Medical Specialty Society

British Menopause Society - Nonprofit Organization

European Menopause and Andropause Society - Professional Association

European Society of Endocrinology - Medical Specialty Society

International Menopause Society - Nonprofit Organization

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from The Endocrine Society Web site .

Availability of Companion Documents

The following are available:

- Mohammed K, Abu Dabrh AM, Benkhadra K, Al Nofal A, Carranza Leon BG, Prokop LJ, Murad MH. Oral vs. transdermal estrogen and the risk of venous and arterial thrombotic adverse events: a systematic review and meta-analysis. Preliminary Report for the Endocrine Society. 2014 Apr 24. 31 p.
- Asi N, Haydour Q, Gionfriddo M, Morey Vargas OL, Mohammed K, Murad MH. Risk of breast cancer in natural progesterone versus synthetic progestins: a systematic review and meta-analysis. Preliminary Report for the Endocrine Society. 2014 Apr 24. 17 p.
- Benkhadra K, Mohammed K, Al Nofal A, Alahdab F, Carranza Leon BG, Zuniga J, Abu Dabrh AM, Murad MH. Hormonal replacement therapy and mortality: a systematic review and meta-analysis. Preliminary Report for the Endocrine Society. 2014 Apr 25. 95 p.

Patient Resources

None available

NGC Status

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